US Patent Application No. 10/506805
Filed 19 January 2005
Inventor LEWIS, Andrew Lennard *et al.*
Attorney Docket: Q83534
Examiner: Purdy, Kyle A.

35 U.S.C. 1.132 DECLARATION

I, Andrew Lennard Lewis, a UK citizen of Biocompatibles UK Limited, Chapman House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL, UK, declare as follows:

1. I am the same Andrew Lennard Lewis as has submitted a declaration in the present Application, dated 7 January 2008. I have read the Office Action dated 6 November 2009, and I am aware of the correspondence to and from the USPTO in between the submission of my first declaration and this most recent Office Action.

2. The Examiner has rejected the current claims as being obvious over Lobb et al., in view of Kataoka evidenced by Dalmark. I have read the Examiner's comments on the response submitted to the previous Office Action, in Sections 7-11 of the Office Action of 6 November 2009. I have also further reviewed the grounds for rejection set out in Sections 12-20 of the Office Action. The polymers used in Lobb et al., are different to those required by claim 1 of the present Application in terms of the nature of the hydrophobic comonomer used to form the block copolymer. As the Examiner acknowledges, Lobb et al., uses DEA monomer while the present claims require use of the monomer DPA.

3. *In vitro* assays have indicated that these diblock copolymers comprising DPA have negligible cytotoxicities whereas those comprising DEA are cytotoxic. This could not have been expected from the prior art.

4. The cytotoxicity assay data is explained clearly in a paper annexed hereto (Exhibit ALL1) by Salvage *et al.* I am one of the co-authors. Indeed all three co-inventors on the present Application are co-authors of this publication. The publication includes some of the data and experiments set out in the present specification. However there are some additional results and the conclusions drawn are not all mentioned in the present specification.

5. The Examiner's attention is drawn to Figure 9 which shows the cytotoxic effect of MPC-DEA and MPC-DPA block copolymers. V79 cells are used. The cytotoxity studies are described in detail in paragraph 2.7 on page 263.

6. It can be seen from Exhibit ALL1 that there is a dramatic difference between the reduction in colony formation, even at relatively low concentrations, for the MPC-DEA block copolymers and that for the MPC-DPA block copolymers. For the latter copolymers the effect (i.e. the cytotoxicity) is only shown at a concentration three orders of magnitude higher than for MPC-DEA. This would suggest the MPC-DPA block copolymers should be worthy of further exploration as drug delivery materials.

7. Quoting from the abstract, the paper concludes

"The MPC-DEA diblock copolymers formed micelles at around pH 8 and longer DEA-block lengths allowed higher drug loadings. However these micelles were not stable at physiological pH. In contrast, MPC-DPA diblock copolymers formed micelles of circa 30 nm diameter of physiological pH. In vitro assays indicated that these MPC-DPA diblock copolymers had negligible cytotoxicities."

8. The Salvage reference uses a standard cytotoxicity assay which is well recognised in the field and allows one to draw general conclusions about the cytotoxic effects of compounds under examination. As detailed above, V79 cells are used. Annexed hereto as Exhibit ALL2 is International Standard ISO 10993-5, Part 5, which describes standard tests for *in vitro* cytotoxicity. I refer for instance to page 5, under section 5:

"Established cell lines are preferred and where used shall be obtained from recognised repositories (3)".

Footnote 3 states "For example....V-79 379A are endorsed by ISO experts to be suitable".

9. I also refer to page 19, Annex B- Colony Formation Cytotoxicity Test, wherein the use of V79 cells is described in detail. In Section B.2.2.1 it is stated "NOTE V79 cells are recommended because they make large and clear colonies...."

10. Accordingly, it is clear that V79 cell assay is a well recognised means for establishing cellular cytotoxicity.

11. I acknowledge that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. 1001) and may jeopardise the validity of the Application or any Patent issuing thereon. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true.

Dated this 1st day of October 2010

Andrew Lennard Lewis